Synthetic Application of Azetidin-2-ones to a Synthesis of Furan Derivatives

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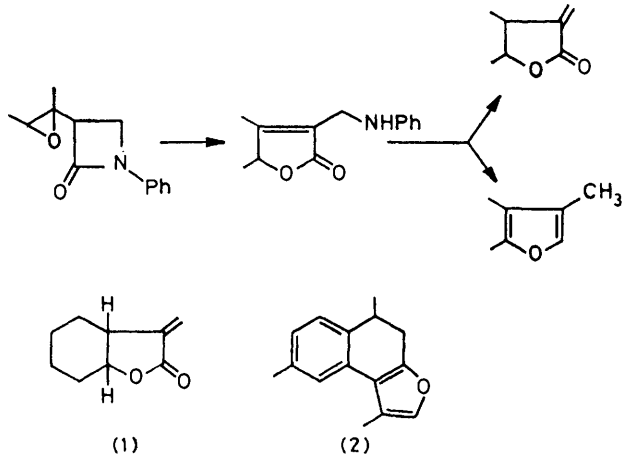
2-(1-Anilinoethyl)but-2-enolides (8a and b) were synthesized from 4-methyl-1-phenylazetidin-2-one and the appropriate ketones. In the same way, 2-(1-anilinobutyl)but-2-enolides (12a and b) were obtained by the use of 1-phenyl-4-propylazetidin-2-one. These butenolides were converted into the corresponding furan derivatives by reduction with di-isobutylaluminium hydride. Phenylation of the butenolides with phenyl-lithium or phenylmagnesium bromide yielded the corresponding 2-phenylfuran derivatives. Furthermore, 3-anilinomethyl-2-methyl- and -ethyl-4,5,6,7-tetrahydrobenzo[*b*]furan were obtained from the butenolide (15) with methyl- or ethylmagnesium iodide, respectively.

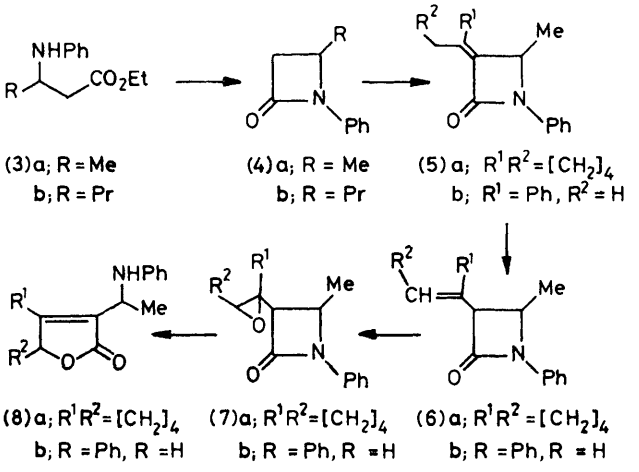
DURING an investigation of the utility of azetidin-2-ones as starting materials for synthesising heterocyclic compounds,[1-3] we found that 3-oxiranylazetidin-2-ones were easily converted into 2-anilinomethylbut-2-enolides [4,5] by treatment with methanesulphonic acid in benzene under reflux. These butenolides were found to be useful intermediates leading to α-methylene-γ-lactones [4] and 3-methylfurans.[6] By this method, the bicyclic lactone (1) [4] and (±)-laevigatin (2) [6] were synthesized. In



SCHEME 1

view of their unique functionality, 2-anilinomethylbut-2-enolides would be expected to serve as a useful intermediates for elaboration of furan derivatives. We have successively explored a general synthetic method for the synthesis of furan derivatives *via* 2-anilinoalkylbut-2-enolides, prepared from 4-alkylazetidin-2-ones and the appropriate ketones.

Condensation of 4-methyl-1-phenylazetidin-2-one (4a)[7] [prepared by cyclisation of ethyl β-anilinobutyrate (3a)] with cyclohexanone by the method previously reported,[4] afforded 3-cyclohexylidene-4-methyl-1-phenylazetidin-2-one (5a). Treatment of (5a) with lithium di-isopropylamide (LDA) in tetrahydrofuran at 0 °C gave the isomerized product (6a) in 85% yield. Oxidation of (6a) with *m*-chloroperbenzoic acid at room temperature afforded the epoxide (7a), treatment of which with methanesulphonic acid in benzene under reflux yielded the 2-(1-anilinoethyl)but-2-enolide (8a). The lactone (8b) was prepared similarly from (4a) and acetopenone (Scheme 2).

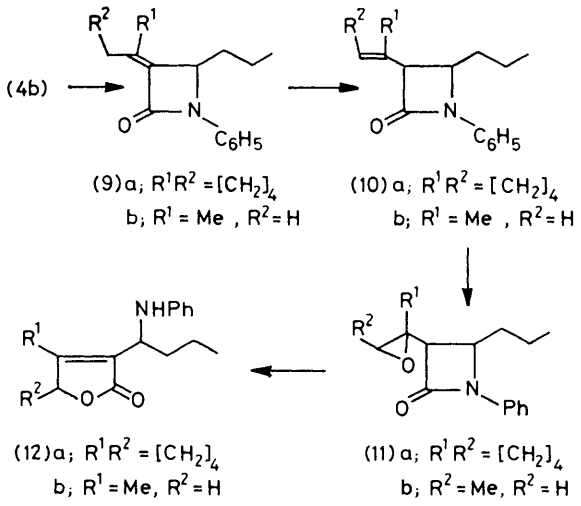


SCHEME 2

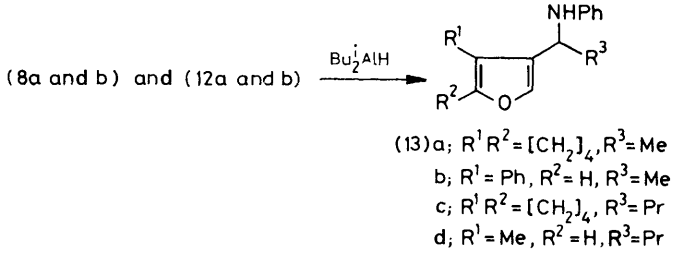
The 2-(1-anilinobutyl)but-2-enolides (12a and b) were obtained similarly from 1-phenyl-4-propylazetidin-2-one (4b) [prepared by cyclisation of the ester (3b)] as outlined in Scheme 3.

Reactions of the butenolides are exemplified by their reduction and alkylation to give furan derivatives. Reduction of (8a) with di-isobutylaluminium hydride [8] in toluene at −78 °C afforded 3-(1-anilinoethyl)-4,5,6,7-tetrahydrobenzo[*b*]furan (13a). In a similar way, the butenolides (8b), (12a), and (12b) were reduced to the furan derivatives (13b—d), respectively. These were characterized by high resolution mass spectra (Table 1).

Phenylation of (8a) and (12a) by phenyl-lithium in tetrahydrofuran at −78 °C gave the tetrahydrobenzo-[*b*]furans (14a and b), respectively. In order to establish the generality of this phenylation, the butenolide (15) [4] was also treated with phenyl-, 4-methoxyphenyl-, and 4-methylphenyl-lithium to give the corresponding 2-arylfuran derivatives (17)—(19), respectively. Phenylation of (16) [4] with phenyl-lithium afforded 3-anilinomethyl-5-methyl-2,4-diphenylfuran (20). Arylation and



SCHEME 3



SCHEME 4

3-(1-Anilinoalkyl)furans (13)

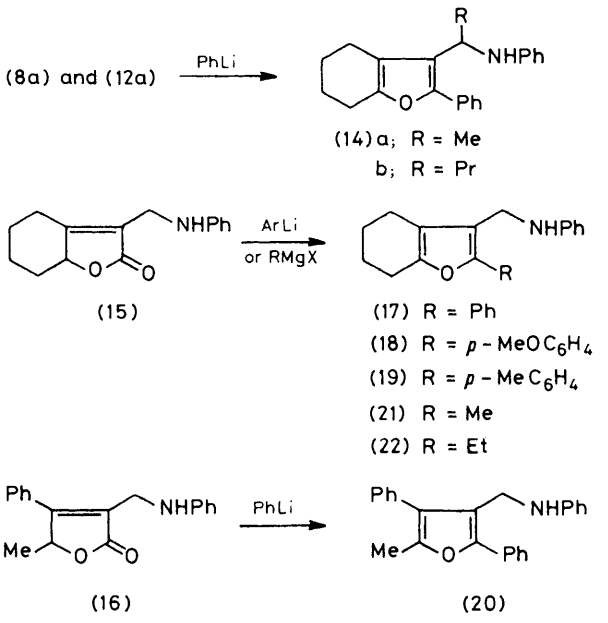
Compd.	Yield (%)	Formula	M^+ (calc.)	δ (CCl_4) for R^3CH
(13a)	93	$C_{16}H_{19}NO$	241.1474 (241.1466)	4.34 (1 H, q, *J* 6.5 Hz)
(13b)	93	$C_{18}H_{17}NO$	263.1331 (263.1310)	4.55 (1 H, q, *J* 6 Hz)
(13c)	94	$C_{18}H_{23}NO$	269.1779 (269.1779)	4.18 (1 H, t, *J* 6 Hz)
(13d)	91	$C_{15}H_{19}NO$	229.1466 (229.1452)	4.19 (1 H, t, *J* 6 Hz)

alkylation by Grignard reagents were also examined. The reaction of (15) with phenylmagnesium bromide also gave (17). Methylation of (15) with methylmagnesium iodide yielded 3-anilinomethyl-2-methyl-4,5,6,7-tetrahydrobenzo[*b*]furan (21) and ethylation with ethylmagnesium bromide gave the corresponding 2-ethyl derivative (22).

Thus, 4-substituted azetidin-2-ones were found to serve in a general method for preparation of polysubstituted furan derivatives; the anilino-group is removable as illustrated in the synthesis of (±)-menthofuran and (±)-laevigatin (2).[6]

EXPERIMENTAL

N.m.r. spectra were recorded with a Varian spectrometer (60 MHz), with tetramethylsilane as internal standard. Mass spectra were obtained with a Hitachi RMU-7L spectrometer. All reactions were carried out under a nitrogen



SCHEME 5

atmosphere. Tetrahydrofuran (THF) was dried and distilled from $LiAlH_4$ before use.

4-Methyl-1-phenylazetidin-2-one (4a).—To a stirred solution of ethyl β-anilinobutyrate (20.7 g, 0.1 mol) in THF (250 ml) was added a solution of ethylmagnesium bromide (33.4 ml of 3M-solution in ether) at room temperature. Stirring was continued for 12 h, the solution was evaporated and the mixture diluted with water and extracted with chloroform. Insoluble material was filtered off and the organic layer was washed with water, dried (Na_2SO_4), and evaporated to leave (4a) (9.9 g, 61%) as an *oil*, b.p. 112—117 °C (1.5 Torr) (Found: C, 74.6; H, 7.1; N, 8.7. $C_{10}H_{11}NO$ requires C, 74.5; H, 6.9; N, 8.95%); δ($CDCl_3$) 1.49 (3 H, d, *J* 6 Hz), 2.60 (1 H, dd, *J* 2.5 and 15.5 Hz), and 3.21 (1 H, dd, *J* 5.5 and 15.5 Hz); *m/z* 161 (M^+).

1-Phenyl-4-propylazetidin-2-one (4b).—To a stirred solution of ethyl 3-anilinohexanoate (23.5 g, 0.1 mol) in THF (300 ml) was added a solution of ethylmagnesium bromide (33.4 ml of 3M-solution in ether). Stirring was continued for 12 h, then the mixture was worked up as above to give the *azetidinone* (4b) (11.3 g, 60%), b.p. 119—121 °C (1 Torr), m.p. 41—42.5 °C (benzene–hexane) (Found: C, 75.9; H, 8.15; N, 7.25. $C_{12}H_{15}NO$ requires C, 76.15; H, 8.0; N, 7/05%); δ($CDCl_3$) 2.65 (1 H, dd, *J* 3 and 15 Hz) and 3.16 (1 H, dd, *J* 5 and 15 Hz); *m/z* 189 (M^+).

General Procedure for the Preparation of 3-Alkylidene-1-phenylazetidin-2-ones (5a and b) *and* (9a and b).—To a stirred solution of 2.2 equiv. of LDA [from di-isopropylamine (2.22 g) and a 1.5M-solution of Bu^nLi in hexane (14.8 ml) in THF (40 ml) at −78 °C] was added a solution of the azetidinone (4) (1 equiv., 10 mmol) in THF (20 ml) at −78 °C. After 5 min, to this solution was added chloro(trimethyl)-silane (1.12 g, 11 mmol) at the same temperature. Stirring was continued for 10 min, then a solution of the appropriate ketone (10 mmol) in THF (10 ml) was added. After 15 min, the mixture was poured into aqueous ammonium chloride, warmed at 40 °C for 20—30 min, and extracted with chloroform. The extract was washed with water and dried (Na_2SO_4). Evaporation afforded the product (5) or

(9). 3-*Cyclohexylidene*-4-*methyl*-1-*phenylazetidin*-2-*one* (5a) (1.59 g, 66%) had m.p. 108—109 °C (benzene–hexane) (Found: C, 79.8; H, 7.8; N, 5.85. $C_{16}H_{19}NO$ requires C, 79.65; H, 7.95; N, 5.8); δ($CDCl_3$) 1.53 (3 H, d, *J* 6.5 Hz) and 4.54 (1 H, dd, *J* 6 and 12 Hz); *m/z* 241 (M^+). 4-*Methyl*-3-(α-*methylbenzylidene*)-1-*phenylazetidin*-2-*one* (5b) (1.87 g, 71%) had m.p. 114—115 °C (benzene–hexane) (Found: C, 82.05; H, 6.65; N, 5.25. $C_{18}H_{17}NO$ requires C, 82.1; H, 6.5; N, 5.3%); δ($CDCl_3$) 1.23 (3 H, d, *J* 6 Hz), 2.53 (3 H, s), and 4.89 (1 H, dd, *J* 6 and 11.5 Hz); *m/z* 263 (M^+). 3-*Cyclohexylidene*-1-*phenyl*-4-*propylazetidin*-2-*one* (9a) (1.61 g, 60%) had m.p. 75—76 °C (benzene–hexane) (Found: C, 80.2; H, 8.65; N, 5.2. $C_{18}H_{23}NO$ requires C, 80.25; H, 8.6; N, 5.2%); δ($CDCl_3$) 4.63 (1 H, t, *J* 4 Hz); *m/z* 269 (M^+). 3-*Isopropylidene*-1-*phenyl*-4-*propylazetidin*-2-*one* (9b) (1.35 g, 59%) had m.p. 80—82 °C (benzene–hexane) (Found: C, 78.35; H, 8.6; N, 6.15. $C_{15}H_{19}NO$ requires C, 78.55; H, 8.35; N, 6.1%); δ($CDCl_3$) 1.80 (3 H, s), 2.13 (3 H, s), and 4.61 (1 H, t, *J* 3.5 Hz); *m/z* 229 (M^+).

General Procedure for the Isomerization of the Azetidinones (5) *and* (9) *to* (6) *and* (10).—To a stirred solution of 1.1 equiv. of LDA [from di-isopropylamine (1.11 g) and a 1.5M-solution in hexane of Bu^{n}Li (7.4 ml), in THF] was added a solution of (5) or (9) (10.0 mmol) in THF (20 ml). Stirring was continued for 15 min at 0 °C, then the solution was quenched with t-butyl alcohol at −78 °C. The mixture was diluted with water and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave (6) [or (10)] as an oil. 3-*Cyclohex*-1-*enyl*-4-*methyl*-1-*phenylazetidin*-2-*one* (6a) was obtained in 85% yield (2 g); δ($CDCl_3$) 1.52 (3 H, d, *J* 6.5 Hz) and 5.73 (1 H, m); *m/z* 241 (M^+). 3-(1-*Phenylvinyl*)-4-*methyl*-1-*phenylazetidin*-2-*one* (6b) was obtained in 80% yield (2.1 g); δ($CDCl_3$) 5.44—5.77 (2 H, m); *m/z* 263 (M^+). 3-*Cyclohex*-1-*enyl*-1-*phenyl*-4-*propylazetidin*-2-*one* (10a) was obtained in 82% yield (2.2 g); δ($CDCl_3$) 5.75 (1 H, m) (Found: M^+, 269.180 1. $C_{18}H_{23}NO$ requires *M*, 269.177 9). 3-(1-*Methylvinyl*)-1-*phenyl*-4-*propylazetidin*-2-*one* (10b) was obtained in 80% yield (1.83 g); δ($CDCl_3$) 1.82 (3 H, s) and 4.88—5.05 (2 H, m) (Found: M^+, 229.145 6. $C_{15}H_{19}NO$ requires *M*, 229.145 6).

General Procedure for the Oxidation of the Azetidinones (6) *and* (10) *with* m-*Chloroperbenzoic Acid*.—To a solution of (6) or (10) (10 mmol) in methylene chloride (30 ml) was added *m*-chloroperbenzoic acid (1.19 g, 11 mmol), and the mixture was set aside at room temperature with stirring for 14 h. It was washed with aqueous 5% sodium hydrogen carbonate and water and dried (Na_2SO_4). Evaporation left the corresponding epoxide (7) or (11) as an oil, which was used for the following reaction without purification.

General Procedure for the Preparation of 2-(1-*Anilinoalkyl*)*but*-2-*enolides* (8) *and* (12).—A mixture of methanesulphonic acid (1 ml), benzene (5 ml), and (7) or (11) (1 mmol) was heated for 1.5 h under reflux. The mixture was made basic with 28% ammonia and extracted with chloroform. The extract was washed with water and dried (Na_2SO_4). Removal of the solvent left (8) or (12). 2-(1-*Anilinoethyl*)*but*-2-*enolide* (8a) was obtained in 62% yield (160 mg), m.p. 146—149 °C (benzene–hexane) (Found: C, 74.8; H, 7.35; N, 5.35. $C_{16}H_{19}NO_2$ requires C, 74.7; H, 7.45; N, 5.45%); δ($CDCl_3$) 1.57 (3 H, d, *J* 7.5 Hz) and 4.30—4.69 (2 H, m); *m/z* 257 (M^+). 2-(1-*Anilinoethyl*)-3-*phenylbut*-2-*enolide* (8b) was obtained in 54% yield (151 mg), m.p. 153—155 °C (benzene–ether) (Found: C, 77.45; H, 6.15; N, 5.15. $C_{18}H_{17}NO_2$ requires C, 77.4; H, 6.15; N, 5.0%); δ($CDCl_3$) 1.64 (3 H, d, *J* 6 Hz), 4.53—4.88 (1 H, m), 5.07 (1 H, d, *J* 16 Hz), and 4.73 (1 H, d, *J* 16 Hz); *m/z* 279 (M^+). 2-(1-*Anilinobutyl*)*but*-2-*enolide* (12a) was obtained in 55% yield (157 mg) as an oil; δ($CDCl_3$) 4.32 (1 H, t, *J* 8 Hz) and 4.23—4.67 (1 H, m) (Found: M^+, 285.175 7. $C_{18}H_{23}NO_2$ requires *M*, 285.172 9). 2-(1-*Anilinobutyl*)-3-*methylbut*-2-*enolide* (12b) was obtained in 53% yield (130 mg) as an oil; δ($CDCl_3$) 2.06 (3 H, s), 4.32 (1 H, t, *J* 7 Hz), and 4.51 (2 H, s) (Found: M^+, 245.140 7. $C_{15}H_{19}NO_2$ requires *M*, 245.141 6).

General Procedure for the Reduction of the Lactones (8) *and* (12) *with Di-isobutylaluminium Hydride*.—To a solution of (8) or (12) (1 mmol) in dry toluene (20 ml) was added di-isobutylaluminium hydride (2.13 ml of 20% solution in hexane) at −78 °C with stirring. Stirring was continued for 1.5 h at the same temperature, then the mixture was poured into aqueous ammonium chloride and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4) and evaporated. A solution of the residue in benzene was stirred for 12 h in the presence of 2 g of silica gel at room temperature.[6] The silica gel was removed by filtration, the filtrate was evaporated, and the residual oil chromatographed on silica gel (2 g). Elution with benzene afforded the furan (13). The yields are shown in the Table.

General Procedure for the Alkylation of the Butenolides (8a), (12a), (15), *and* (16).—To a solution of the butenolide (1 mmol) in THF (12 ml) was added the alkylating reagent (2 equiv. of the aryl-lithium, phenylmagnesium bromide, methylmagnesium iodide, or ethylmagnesium bromide) in ether at −78 °C with stirring. Stirring was continued for 1 h at the same temperature, then the mixture was further stirred at 0 °C for 1 h and at room temperature for 10 h. The mixture was poured into water and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give the corresponding furan derivatives. 3-(2-*Anilinoethyl*)-2-*phenyl*-4,5,6,7-*tetrahydrobenzo*[b]*furan* (14a) was obtained in 69% yield (219 mg) as an oil; δ(CCl_4) 1.55 (3 H, d, *J* 7 Hz) and 4.72 (1 H, d, *J* 7 Hz) Found: M^+, 317.177 0. $C_{22}H_{23}NO$ requires *M*, 317.178 0). 3-(1-*Anilinobutyl*)-2-*phenyl*-4,5,6,7-*tetrahydrobenzo*[b]*furan* (14b) was obtained in 64% yield (224 mg) as an oil; δ($CDCl_3$) 4.58 (1 H, d, *J* 6 Hz); *m/z* 345 (M^+). 3-*Anilinomethyl*-2-*phenyl*-4,5,6,7-*tetrahydrobenzo*[b]*furan* (17) was obtained in 76% yield (230 mg) by using phenyllithium and in 78% yield (236 mg) by using phenylmagnesium bromide; m.p. 104—107 °C (hexane–pentane) (Found: C, 83.0; H, 6.95; N, 4.35. $C_{21}H_{21}NO$ requires C, 83.15; H, 7.0; N, 4.6%); δ(CCl_4) 4.10 (2 H, s); *m/z* 303 (M^+). 3-*Anilinomethyl*-2-(4-*methoxyphenyl*)-4,5,6,7-*tetrahydrobenzo*[b]*furan* (18) was obtained in 68% yield (226 mg), m.p. 115—117 °C (hexane) (Found: C, 79.35; H, 7.1; N, 4.15. $C_{22}H_{23}NO_2$ requires C, 79.25; H, 6.95; N, 4.2%); δ(CCl_4) 3.78 (3 H, s) and 4.06 (2 H, s); *m/z* 333 (M^+).

3-*Anilinomethyl*-2-(4-*methylphenyl*)-4,5,6,7-*tetrahydrobenzo*[b]*furan* (19) was obtained in 68% yield (228 mg), m.p. 115—117 °C (hexane–pentane) (Found: C, 83.5; H, 7.45; N, 4.2. $C_{22}H_{23}NO$ requires C, C, 83.25; H, 7.3; N, 4.4%); δ(CCl_4) 2.15 (3 H, s) and 4.08 (2 H, s); *m/z* 317 (M^+). 3-*Anilinomethyl*-5-*methyl*-2,4-*diphenylfuran* (20) was obtained in 76% yield (258 mg), m.p. 116—117.5 °C (hexane–pentane) (Found: C, 84.95; H, 6.3; N, 3.9. $C_{14}H_{21}NO$ requires C, 84.9; H, 6.25; N, 4.15%); δ(CCl_4) 2.38 (3 H, s) and 4.08 (2 H, s); *m/z* 339 (M^+). 3-*Anilinomethyl*-2-*methyl*-4,5,6,7-*tetrahydrobenzo*[b]*furan* (21) was obtained in 70% yield (169 mg); δ(CCl_4) 2.23 (3 H, s) and 3.88 (2 H, s); *m/z*

241 (M^+). 3-*Anilinomethyl*-2-*ethyl*-4,5,6,7-*tetrahydrobenzo*-[b]*furan* (22) was obtained in 68% yield (173 mg), m.p. 49—51.5 °C (pentane) (Found: C, 79.8; H, 8.45; N, 5.55. $C_{17}H_{21}NO$ requires C, 79.96; H, 8.29; N, 5.5%); δ(CCl_4) 1.18 (3 H, t, *J* 7.5 Hz), 2.56 (2 H, q, *J* 7.5 Hz), and 3.86 (2 H, s) (Found: M^+, 255.163 6. $C_{17}H_{21}NO$ requires *M*, 255.163 5).

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REFERENCES

[1] M. S. Manhas, S. G. Amin, and A. K. Bose, *Heterocycles*, 1976, **5**, 669.
[2] S. Kano, T. Ebata, Y. Denta, S. Hibino, and S. Shibuya, *Heterocycles*, 1977, **8**, 411.
[3] S. Kano, T. Ebata, and S. Shibuya, *Chem. Pharm. Bull.*, 1979, **27**, 2450.
[4] S. Kano, T. Ebata, K. Funaki, and S. Shibuya, *J. Org. Chem.*, 1979, **44**, 3946.
[5] S. Kano, T. Ebata, Y. Yuasa, and S. Shibuya, *Heterocycles*, 1980, **14**, 589.
[6] S. Kano, T. Ebata, and S. Shibuya, *Heterocycles*, 1980, **14**, 13.
[7] R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.*, 1949, **71**, 2129.
[8] E. Winterfeldt, *Synthesis*, 1975, 617, and references cited therein.